REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Applicants have amended the specification by incorporating the amendments presented on May 15, 2003, in a substitute sheet (see attached page 9).

At the time of captioned Office Action, claims 26-205 were pending in the application. Claims 26-169 and 178-205, drawn to a non-elected invention, remain withdrawn from further consideration.

Without acquiescing to the propriety of the Examiner's rejections, Applicants have amended claims 170 and cancelled claims 171-172.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier. These amendments do not go beyond the original disclosure of the application.

Upon entry of these amendments, claims 26-170 and 173-205 will be pending.

Statutory Type Double Patenting Rejection

The Examiner contends that dependent claims 171 and 172 are "substantial duplicates of and do not further limit the invention of independent claim 170."

To obviate this rejection, Applicants have cancelled claims 171 and 172 and amended claim 170. Accordingly, the rejection should be withdrawn.

Rejection Under 35 U.S.C. § 101

Under this rejection, the Examiner alleges that the claimed invention lacks patentable utility on the ground that the specification fails to provide any guidance with respect to the function of TSAP-21 and evidence to demonstrate that TSAP 21 is a tumor suppressor gene.

In response, Applicants have amended claim 170 to recite "an isolated DNA molecule encoding TSAP 21, wherein the expression of said TSAP 21 is activated by p53- or p21-induced apoptosis or tumor suppression."

As discussed in the previous response, the inventors had isolated the claimed DNA molecule, TSAP-21, from tumor-suppressed p53-expressing K562 revertants (see Abstract of Roperch *et al.*, *Proc. Natl. Acad. Sci. USA* **96**:8070-8073, 1999). In addition, the inventors found that TSAP-21 displays a sequence homology with an N-ethylmaleimide-sensitive factor-attachment protein receptor (SNARE) family member, syntaxin 11 (see Abstract and page 8071 of Roperch *et al., supra*).

In fact, the inventors have observed the differential expression of TSAP-21 in four different model systems, namely, (i) the K562/KS cells, exemplifying p53-dependent regulation; (ii) the U937/US cells, exemplifying p53-independent regulation; (iii) the US397/p21 cells, exemplifying p21-dependent regulation; and (iv) the human SIAH-1-transfected U937 cells, exemplifying SIAH-1 dependent regulation. As stated by Roperch *et al.*, "it is important to note that all four model systems has in common a suppression of the malignant phenotype and/or activation of programmed cell death" (see page 8971, right column, sixth line from the bottom of the paragraph before Table 1).

Roperch *et al.* also indicate that TSAP-21 is differentially expressed in all of the tested cell model systems (see Table 1). On this basis, the inventors deduced that "the striking overlaps in differential expression of these genes in the different model systems suggest that at least those sharing expression may be part of the tumor suppression and programmed cell death process" (Roperch *et al.* (*supra*) at page 8072, right column, line three).

Furthermore, Applicants enclose a sequence alignment of the claimed TSAP-21 and syntaxin 11 (see Appendix A), as evidence to support their arguments below.

TSAP 21 gene is shorter than syntaxin 11 cDNA present in the database but is identical to syntaxin 11 (see specification at Table 1, page 15). Syntaxin 11 has a role in regulating intracellular trafficking, distribution, and restriction of molecules to specific membrane compartments (see Roperch *et al. supra*, at page 8073, first full paragraph).

Because of its sequence similarity with syntaxin, the claimed TSAP 21 gene may have similar functions with syntaxin. Moreover, the inventors of the instant application discovered that TSAP 21 is differentially expressed in tumor revertant cell lines (e.g., KS cells having a suppressed transformed phenotype, see specification at page 17-18 and Roperch *et al. supra*).

Furthermore, the specification teaches that the absence of TSAP-21 is indicative of cancer susceptibility (specification at page 4, lines 10-25). It can therefore be used as a cancer marker or molecular fingerprint in different tumor-suppression models (see Roperch *et al., supra*). As currently amended, TSAP-21 expression is induced during p53- or p21-induced apoptosis and/or tumor suppression. The specification and amended claims also disclose how the nucleotide sequence of SEQ ID NO:13 can be used as a nucleotide probe, an amplification primer or a diagnostic agent for determining the predisposition of cancer.

Accordingly, a specific, substantial and credible use is disclosed in the claimed invention. Therefore, in view of the above arguments, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejects the pending claims and alleges that the specification fails to describe the subject matter of the pending claims in such a way as to enable one skilled in the art to practice the claimed invention.

Applicants submit that the specification is objectively enabling for the full scope of the claims. Claims 170 has been amended while claims 171-172 have been cancelled. The specification also discloses a substantial and credible utility for TSAP-21, a utility which has been confirmed in the above cited peer-reviewed journal.

In view of the above, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner considers claims 170-172 as indefinite because these claims only describe how the TSAP 21 DNA is produced and do not define the structure or function of the claimed DNA.

In response to the rejection, Applicants have amended claims 170 and cancelled claims 171 and 172. In addition, as remarked above, the specification teaches that the absence of TSAP-21 is analytic of cancer susceptibility (specification at page 4, lines 10-25). Thus, TSAP 21 can be used as a cancer marker or molecular fingerprint in different tumor-suppression models (see Roperch *et al.*, *supra*).

In addition, claim 170 has been amended to recite that TSAP-21 expression is induced during p53- or p21-induced apoptosis and/or tumor suppression. Therefore, this claim does describe a function for TSAP-21. Accordingly, Applicants respectfully request the reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Dec. 1, 2003 By _____

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possible to envisage novel modes of action on the abovementioned sequences for, for example, therapeutic or diagnostic purposes.

~~**Figure 1 represents the extended TSAP 13 sequence (SEQ ID No. 5). The underlined portion corresponds to the sequence as originally brought to light by the inventors. The bold characters correspond to the sequence having 100% homology with the p40.5 subunit of the 26S human proteasome.**~~

~~**Figure 2 represents the extended TSAP 21 sequence (SEQ ID No. 13). The underlined portion corresponds to the sequence as originally brought to light by the inventors. The bold characters correspond to the sequence having 100% homology with syntaxin 11 of the group of SNARE proteins.**~~

Other characteristics of the invention will become apparent upon reading the example below.

MATERIALS AND METHODS

Cell cultures

K562, KS, K52 and K53 cells were used as models. The K562 line is a tumor line derived from a chronic leukemia of erythromyeloid type. It is characterized in particular by a Philadelphia chromosome which contains the translocation (9,22) in which there is a rearrangement of the bcr gene with the abl proto-oncogene. This line has, moreover, an abnormal karyotype and overexpresses the myc and pim-1 oncogenes. These lines are described in the reference A. Telerman et al.: A model for tumor suppression using H-1 parvovirus, Proc. Natl. Acad. Sci. USA. Vol. 90, pp. 8702-8706, September 1993.

In summary, a monoclone of K562 was infected with the H-1 parvovirus. This infection caused a massive death of the cell culture. After maintaining this culture for a period of two months, the KS clone was isolated. The same experiment carried out a second time provided, after three

APPENDIX A

CLUSTAL W (1.82) multiple sequence alignment

```
gi|5441365|emb|AJ012506.1|HomoTSAP21 ----------------------------------------------------
gi|4507286|ref|NM_003764.1|Syntaxin CGCGGCGGCGCGGAGCTCGGGCGGCCGTGGAGGAACTCAGCCTCGGCCGC 50

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          AGGAGGCGCCGGGAGCGGAGCCGCCGGGAGTCGCGCAACAGGTTTCCTTC 100

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          TCCATCCGTGCGCCCACAGGGGACGCGCGCCCTGCCGGGAGAGGGGCTTC 150

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          TCGGTTCGCACTCTCGCTCCCAGTCCAGGCAAAATGAAAGACCGGCTAGC 200

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          AGAACTTCTGGACTTGTCCAAGCAATATGACCAGCAGTTCCCAGACGGGG 250

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          ACGATGAGTTTGACTCGCCCCACGAGGACATCGTGTTCGAGACGGACCAC 300

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          ATCCTGGAGTCCCTGTACCGAGACATCCGGGACATTCAGGATGAAAACCA 350

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          GCTGCTGGTGGCCGACGTGAAGCGGCTGGGAAAGCAGAACGCCCGCTTCC 400

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          TCACGTCCATGCGGCGCCTCAGCAGCATCAAGCGCGACACCAACTCCATC 450

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          GCCAAGGCCTTCAGGGCCCGGGGCGAGGTCATCCACTGCAAGCTGCGCGC 500

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          CATGAAGGAGCTGAGCGAGGCGGCTGAGGCCCAGCACGGCCCGCACTCGG 550

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
gi|4507286|ref|NM_003764.1|          CAGTGGCGCGCATTTCGCGGGCGCAGTACAACGCGCTCACCCTCACCTTC 600

gi|5441365|emb|AJ012506.1|Homo       ----------------------------------------------------
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```
gi|4507286|ref|NM_003764.1|          CAGCGCGCCATGCACGACTACAACCAGGCCGAGATGAAGCAGCGCGACAA 650


gi|5441365|emb|AJ012506.1|Homo       ------------ATCCAGCGCCAGCTGGAGATCATGGGCAAGGAAGTCT 37
gi|4507286|ref|NM_003764.1|          CTGCAAGATCCGCATCCAGCGCCAGCTGGAGATCATGGGCAAGGAAGTCT 700
                                     ************************************


gi|5441365|emb|AJ012506.1|Homo       CGGGCGACCAGATCGAGGACATGTTCGAGCAGGGTAAGTGGGACGTGTTT 87
gi|4507286|ref|NM_003764.1|          CGGGCGACCAGATCGAGGACATGTTCGAGCAGGGTAAGTGGGACGTGTTT 750
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       TCCGAGAACTTGCTGGCCGACGTGAAGGGCCGCGCGGGCCGCCCTCAACG 137
gi|4507286|ref|NM_003764.1|          TCCGAGAACTTGCTGGCCGACGTGAAGGGCCGCG--GGCCGCCCACAACG 798
                                     ************************************  ******** *****


gi|5441365|emb|AJ012506.1|Homo       AGATCGAGAGCCGCCACCGCGAACTGCTGCGCCTGGAGAGCCGC-ATCCG 186
gi|4507286|ref|NM_003764.1|          AGATCGAGAGCCGCCACCGCGAACTGCTGCGCCTGGAGAGCCGCCATCCG 848
                                     ******************************************** *****


gi|5441365|emb|AJ012506.1|Homo       CGACGTACACGAGCTCTTCTTGCAGATGGCGGTGCTGGTGGAGAAGCAGG 236
gi|4507286|ref|NM_003764.1|          CGACGTACACGAGCTCTTCTTGCAGATGGCGGTGCTGGTGGAGAAGCAGG 898
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       CCGACACCCTGAACGTCATCGAGCTCAACGTACAAAAGACGGTCGACTAC 286
gi|4507286|ref|NM_003764.1|          CCGACACCCTGAACGTCATCGAGCTCAACGTACAAAAGACGGTCGACTAC 948
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       ACCGGCCAGGCCAAGGCGCAGGTGCGGAAGGCCGTGCAGTACGAGGAGAA 336
gi|4507286|ref|NM_003764.1|          ACCGGCCAGGCCAAGGCGCAGGTGCGGAAGGCCGTGCAGTACGAGGAGAA 998
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       GAACCCCTGCCGGACCCTCTGCTGCTTCTGCTGTCCCTGCCTCAAGTAGC 386
gi|4507286|ref|NM_003764.1|          GAACCCCTGCCGGACCCTCTGCTGCTTCTGCTGTCCCTGCCTCAAGTAGC 1048
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       AGGCCGGCCCGGGCCGCCACCGCCCATCCCAGACCATGGAGCGCGCTGGG 436
gi|4507286|ref|NM_003764.1|          AGGCCGGCCCGGGCCGCCACCGCCCATCCCAGACCATGGAGCGCGCTGGG 1098
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       AAGGACGTCACCAAAGCCGGGAGCTCTGCCCTGCAGGGAGTTGCCCCAAC 486
gi|4507286|ref|NM_003764.1|          AAGGACG-CACCAAAGCCGGGAGCTCTGCCCTGCAGGGAGTTGCCCCAAC 1147
                                     ******* ******************************************


gi|5441365|emb|AJ012506.1|Homo       CCTTTCCGGAACTCAGTCTTTAGAAAAGAAACGCCAGGTTCAAGAATTGC 536
gi|4507286|ref|NM_003764.1|          CCTTTCCGGAACTCAGTCTTTAGAAAAGAAACGCCAGGTTCAAGAATTGC 1197
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       AAACCAGCCTGTGCTTGGAAAGATGGTTAGTTGATACCGTCCGATGATTC 586
gi|4507286|ref|NM_003764.1|          AAACCAGCCTGTGCTTGGAAAGATGGTTAGTTGATACCGTCCGATGATTC 1247
                                     **************************************************


gi|5441365|emb|AJ012506.1|Homo       TTCAGTAAAGATAGATTCCCACAAAGTTGTGCAATGTCATTATATGACAC 636
```

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gi|4507286|ref|NM_003764.1|          TTCAGTAAAGATAGATTCCCACCTCGTGCCGAA---------------- 1280
                                     ********************   **   * *

gi|5441365|emb|AJ012506.1|Homo       CTTGCACTCTTACCGTCTTGACAGAAGCCAAGTAAGGAACTGAAGTTGTA 686
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TCTGACTGTAGGGTGAATGTCTGAGGCCTGCCTCCTAATAAAGACTCAAG 736
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       GAGGAAGTCAATTGGGCATCTGCTAATAGAATGAACTCATGATGGAAACT 786
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TCAGTTCATTTACTTTGTCCCTGAAAATTCCCTGGTTCTGTTCCATTTTG 836
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       AGCGAAATTGGCCTTGGGAAAAACCACGTTCTTCCTTTCCGATTCTTCAT 886
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       CCGGTCTACGGCTATGCAATTCCTCCCCAAATATAGATCTTATTTCTGCT 936
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       CATTTCCCCTACTTATTAAAATCACACCAAACACTTACTATTTTCTTATC 986
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TCTTTCACTTTTTAAATATCTTTCACCAGGTTATATTTTGGTATTATTTT 1036
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TCCAAACATTTTTAAGCACTGAATATCGAACAAGCACTCAAATTGAAGTA 1086
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TCAGTCATGTTTTGTGTATTTTTCGCTGATAAAAATTATTTAACATTTAT 1136
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       ATTTTTACTTGATTACATATGCACATGTATGTAAATGTAAAATACTAATA 1186
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       TTCACTAATATATGTACATAATGATCAATTGGTTTAACTTCTTTTATGTA 1236
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       AGTATGGTATATAAATTTCAAGACGAAAAAAAAAAAAAAAAAAAAAAAA 1286
```

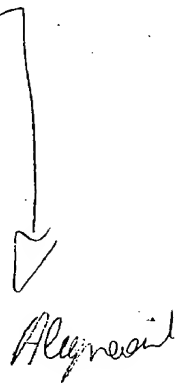
Aln_TSAP21_Syntax

```
gi|4507286|ref|NM_003764.1|          --------------------------------------------------

gi|5441365|emb|AJ012506.1|Homo       AAAAAAAAAA 1296
gi|4507286|ref|NM_003764.1|          ----------
```

name	ACCESSION NUMBER	DESCRIPTION
TSIP1	NM_153088	Mus musculus nuclear LIM interactor-interacting factor 3 (Nif3), mRNA
TSIP2	NM_008943.1	Mus musculus presenilin 1 (Psen1), mRNA
TSIP3	AL451145	AL451145 Human DNA sequence from clone RP11-164A17 on chromosome 6, complete sequence [Homo sapiens]
TSAP1	NM_024353	Rattus norvegicus Phospholipase C , beta4 (Plcb4), mRNA
TSAP2	XM_282593	Mus musculus zinc finger protein 162 (Zfp162), mRNA
TSAP3	XM_008013.3	Homo sapiens seven in absentia (Drosophila) homolog 1 (SIAH1), mRNA
TSAP4	AC092799.2	Homo sapiens chromosome 1 clone RP11-5F19, complete sequence
TSAP5	NM_029418	Mus musculus RIKEN cDNA 9130401M01 gene (9130401M01Rik), mRNA
TSAP6	AY029586.1	Mus musculus dudulin 2 mRNA, complete cds
TSAP7	AP000901.5	AP000901 Homo sapiens genomic DNA, chromosome 11q clone:RP11-686G14, complete sequence
TSAP8	Z62516.1	HS6D10R H.sapiens CpG island DNA genomic Mse1 fragment, clone 6d10
TSAP9	NM_012073	Homo sapiens chaperonin containing TCP1, subunit 5 (epsilon) (CCT5), mRNA
TSAP10	BC000628.1	BC000628 Homo sapiens, clone IMAGE:3343149, mRNA, partial cds
TSAP11	BC017472.1	BC017472 Homo sapiens, clone MGC:10198 IMAGE:3909581, mRNA, complete cds
TSAP12	AC004857.1	AC004857 Homo sapiens PAC clone RP4-685A2 from 7p21-p22, complete sequence
TSAP13	BC001100.1	BC001100 Homo sapiens, proteasome (prosome, macropain) 26S subunit,non-ATPase, 13, clone MGC:734 IMAGE:3506530, mRNA, complete cds
TSAP14	NM_022831.1	Homo sapiens hypothetical protein FLJ12806 (FLJ12806), mRNA
TSAP15	NM_021943	Homo sapiens testis expressed sequence 27 (TEX27), mRNA
TSAP16	AL360157.12	AL360157 Human DNA sequence from clone RP11-801I18 on chromosome 6q14.2-16.1Contains GSSs, complete sequence [Homo sapiens]
TSAP17	AL356475.11	AL356475 Human DNA sequence from clone RP11-332H17 on chromosome 1, complete sequence [Homo sapiens]
TSAP18	AP003351.2	AP003351 Homo sapiens genomic DNA, chromosome 8q23, clone: KB1184D12
TSAP19	AL392024.3	CNS06C8K Human chromosome 14 DNA sequence BAC R-182E21 of library RPCI-11 from chromosome 14 of Homo sapiens (Human), complete sequen
TSAP20		
TSAP21	XM_047153.1	Homo sapiens similar to SYNTAXIN 11 (LOC92766), mRNA
TSAP22	AJ132695.5	HSA132695 Homo sapiens rac1 gene

BLAST le 26/02/2003



Alignement